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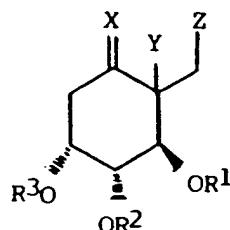
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(54) Cyclohexanetriol derivatives.

(57) Cyclohexanetriol derivatives represented by the formula



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wherein

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same or different, and each denotes a hydrogen atom or a protecting group of a hydroxyl group.

X denotes an oxygen atom, =CHCH<sub>2</sub>OR<sup>4</sup>, =CHCHO or =CHCO<sub>2</sub>R<sup>5</sup>, Y denotes a hydrogen atom and Z denotes -OR<sup>6</sup>, or Y and Z together form a single bond; or X and Z together form =NO-, =CHCH(OR<sup>7</sup>)O- or =CHCO<sub>2</sub>- and Y is a hydrogen atom, R<sup>4</sup> and R<sup>6</sup> denote a hydrogen atom or a protecting group of a hydroxyl group respectively, R<sup>5</sup> denotes a lower alkyl group, and R<sup>7</sup> denotes a hydrogen atom or a lower alkyl group.

Said derivatives are useful as synthetic intermediates of 1-hydroxyvitamin D derivatives.

This invention relates to novel cyclohexanetriol derivatives. More specifically, this invention relates to  $1\alpha, 2\beta, 3\beta$ -cyclohexanetriol derivatives useful as key A-ring synthons to synthesize  $1\alpha$ -hydroxyvitamin D derivatives, especially  $1\alpha$ -hydroxyvitamin D derivatives having a substituent in the  $2\beta$ -position, e.g.,  $2\beta$ -hydroxypropoxy- $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub>.

5 In recent years, with the progress of studies on vitamin D, the above  $1\alpha$ -hydroxyvitamin D derivatives, and many other  $1\alpha$ -hydroxyvitamin D derivatives have been developed as medicaments. In this connection, a convergent synthesis process is useful for not only producing same but also synthesizing metabolites, decomposition products or labeled compounds which are essential in development as medicaments.

10 It has been proposed that  $2\beta$ -hydroxypropoxy- $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub> which is expected to be put to practical use as an osteoporosis treating agent having high blood durability is synthesized by using a steroid compound as a starting material, epoxidizing the A-ring and then opening the epoxide ring to introduce a hydroxyalkoxy group into the 2-position [see, e.g., U. S. Patent No. 4,666,634 (Japanese Laid-open Patent Application (Kokai) No. 267,549/1986)]. However, it suffers drawbacks that a starting material can hardly be obtained and the final step of the process is a photoreaction with a low yield.

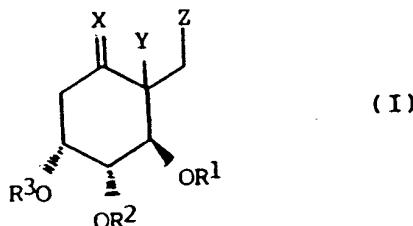
15 As a convergent process for synthesizing  $1$ -hydroxyvitamin D derivatives, there has been reported a process which comprises forming an A-ring synthon of a  $1$ -hydroxyvitamin D derivative by using as a starting material, e.g., (S)-(+)-carvone (J. Org. Chem. 1986, 51, 3098-3108), (R)-(-)-carvone (J. Org. Chem. 1989, 54, 3515-3517), or a cyclohexenedicarboxylic acid ester (Tetrahedron Letters, vol. 31, No. 11, pp. 1577-1580, 1990), and combining it with a CD-ring synthon.

20 These processes have however drawbacks that the starting material is costly, reagents which are industrially hard to obtain and limited in use have to be employed, and a synthesis route up to key intermediates is long and/or intricate; they are thus not necessarily satisfactory in industrial practice.

25 Besides, the processes set forth in the above literature are all concerned with synthesis of a  $1\alpha$ -hydroxyvitamin D derivative having no substituent in the 2-position. A-ring synthons available in synthesis of  $1\alpha$ -hydroxyvitamin D derivatives having a substituent in the 2-position, such as  $2$ -hydroxypropoxy- $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub>, have been so far unknown.

30 It is thus an object of this invention to provide novel cyclohexanetriol derivatives useful in synthesizing  $1\alpha$ -hydroxyvitamin D derivatives, especially  $1\alpha$ -hydroxyvitamin D derivatives having a substituent in the 2-position, which can be produced in relatively short steps using inexpensive starting materials that can easily be obtained.

According to this invention, there are provided cyclohexanetriol derivatives represented by formula (I)



wherein

45  $R^1$ ,  $R^2$  and  $R^3$  are the same or different, and each denotes a hydrogen atom or a protecting group of a hydroxyl group.

X denotes an oxygen atom,  $=CHCH_2OR^4$ ,  $=CHCHO$  or  $=CHCO_2R^5$ , Y denotes a hydrogen atom and Z denotes  $-OR^6$ , or Y and Z together form a single bond; or X and Z together form  $=NO_2$ ,  $=CHCH(OR^7)O-$  or

$=CHCO_2-$  and Y is a hydrogen atom.

50  $R^4$  and  $R^6$  denote a hydrogen atom or a protecting group of a hydroxyl group respectively,  $R^5$  denotes a lower alkyl group, and

$R^7$  denotes a hydrogen atom or a lower alkyl group.

55 The cyclohexanetriol derivatives of formula (I) provided by this invention are useful as synthetic intermediates of  $2\beta$ -hydroxypropoxy- $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub> which is expected to be clinically applied as an osteoporosis treating agent having high blood durability. They are also quite useful as synthetic intermediates of  $1\alpha$ -hydroxyvitamin D derivatives which are deemed effective for treating defective diseases of calcium metabolism, e.g., chronic renal failure, hypoparathyroidism, secondary hyperparathyroidism, osteomalacia and osteoporosis, such as  $1\alpha$ -hydroxyvitamin D<sub>3</sub>,  $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub>,  $1\alpha$ -hydrox-

vitamin D<sub>2</sub>, and 24-*epi*-1 $\alpha$ , 25-dihydroxyvitamin D<sub>2</sub>, and as synthetic intermediates of 1 $\alpha$ -hydroxyvitamin D derivatives which are expected to be effective for treating skin diseases, e.g., psoriasis and diseases caused by abnormal cell differentiation, e.g., myelogenous leukemia, such as 1 $\alpha$ ,24-dihydroxyvitamin D<sub>3</sub>, 22-oxa-1,25-dihydroxyvitamin D<sub>3</sub>, and 22-dehydro-26,27-cyclo-1 $\alpha$ , 24-dihydroxyvitamin D<sub>3</sub>.

5 The word "lower" here referred to means that the number of carbon atoms of a group or a compound to which this word is applied is 6 or less, preferably 4 or less.

The protecting group of the hydroxyl group denoted by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and/or R<sup>6</sup> can be any protecting group which can be removed by a protecting group eliminating means such as hydrolysis or hydrogenolysis. Examples of the protecting group are as follows.

10 (i) an acyl group represented by formula  $R^2CO$  [wherein  $R^2$  denotes a hydrogen atom, or a  $C_1-C_8$  alkyl,  $C_1-C_4$  haloalkyl or aryl group], such as a formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, caprooyl, benzoyl or trifluoroacetyl group.

(ii) an alkoxy carbonyl group represented by formula  $R^bOCO-$  [wherein  $R^b$  denotes a lower alkyl, lower alkenyl,  $C_7-C_8$  aralkyl or aryl group], such as a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl or phenoxy carbonyl group.

(iii) a trisubstituted silyl group represented by formula

(iii) a tri-substituted allyl group represented by formula

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20 R<sup>d</sup> - Si - R<sup>e</sup>

[wherein R<sup>c</sup>, R<sup>d</sup> and R<sup>e</sup> are the same or different, and each denotes a lower alkyl, aryl or C<sub>7</sub>-C<sub>9</sub> aralkyl group], such as a trimethylsilyl, triethylsilyl, triisopropylsilyl, tertbutyldimethylsilyl, tert-butyldiphenylsilyl or tribenzylsilyl group.

(iv) a 1-alkoxymethyl group represented by formula

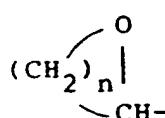
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$$\begin{array}{c} R^g & R^g \\ & \backslash / \\ R^5 & O=C= \end{array}$$

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[wherein R<sup>s</sup> denotes a lower alkyl group that may optionally be substituted by a lower alkoxy group, and R<sup>g</sup> and R<sup>g'</sup> denote a hydrogen atom or a lower alkyl group respectively], such as a methoxymethyl, methoxymethoxymethyl, 1-ethoxethyl or methoxisopropyl group, and

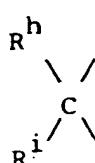
(v) a 2-oxacycloalkyl group represented by formula



[wherein  $n$  is an integer of 3 to 6], such as a tetrahydrofuryl or tetrahydropyanyl group.

Further, R<sup>1</sup> and R<sup>2</sup> or R<sup>2</sup> and R<sup>3</sup> may together form an acetal group represented by formula

58



55

[wherein R<sup>h</sup> and R<sup>i</sup> are the same or different, and each denotes a hydrogen atom, or a lower alkyl, aryl or

$C_7-C_{11}$  aralkyl group], such as an ethylidene, isopropylidene or benzylidene group.

Thus, desirous examples of the protecting group of the hydroxyl group are as follows.

5       $R^1$  and  $R^3$ : an acetyl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, methoxymethyl, methoxyethoxymethyl, 1-ethoxyethyl or tetrahydropyranyl group

10      $R^2$ : an acetyl, pivaloyl, benzoyl, methoxycarbonyl or ethoxycarbonyl group

15      $R^4$ : a tetrahydropyranyl, ethoxyethyl or methoxyisopropyl group

20      $R^6$ : a 1-ethoxyethyl, tetrahydropyranyl, methoxyisopropyl, tert-butyldimethylsilyl or triethylsilyl group

25     Alternatively,  $R^1$  and  $R^2$  can together form an isopropylidene group.

Preferable examples of the protecting group of the hydroxyl group are:

10      $R^1$ : an acetyl, tert-butyldimethylsilyl or tert-butyldiphenylsilyl group

15      $R^2$ : an acetyl or methoxycarbonyl group

20      $R^3$ : an acetyl, methoxymethyl, 1-ethoxyethyl, tert-butyldimethylsilyl or tert-butyldiphenylsilyl group

25      $R^4$ : a tetrahydropyranyl group

30      $R^6$ : a tert-butyldimethylsilyl group

35     Alternatively,  $R^1$  and  $R^2$  can together form an isopropylidene group.

Meanwhile, examples of the lower alkyl group represented by  $R^5$  and  $R^7$  are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl groups. Of these, methyl, ethyl and isopropyl groups are preferable.

40     Among others, the cyclohexanetriol derivatives of formula (I) wherein

45      $R^1$  is a hydrogen atom, or an acetyl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, methoxymethyl, methoxyethoxymethyl, 1-ethoxyethyl or tetrahydropyranyl group,

50      $R^2$  is a hydrogen atom, or an acetyl, pivaloyl, benzoyl, methoxycarbonyl or ethoxycarbonyl group, or

55      $R^1$  and  $R^2$  together form an isopropylidene group, and

60      $R^3$  is a hydrogen atom, or an acetyl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, methoxymethyl, methoxyethoxymethyl, 1-ethoxyethyl or tetrahydropyranyl group are preferable. The cyclohexanetriol derivatives of formula (I)

65     wherein

70      $R^1$  is a hydrogen atom, or an acetyl, tertbutyldimethylsilyl or tert-butyldiphenylsilyl group,

75      $R^2$  is a hydrogen atom, or an acetyl or methoxycarbonyl group, or

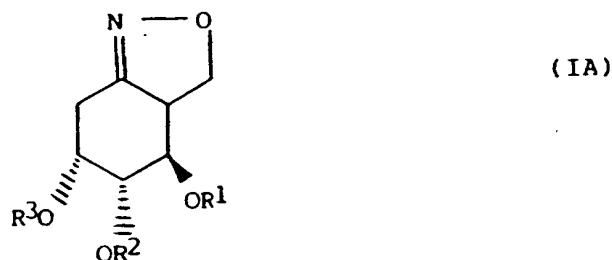
80      $R^1$  and  $R^2$  together form an isopropylidene group,

85      $R^3$  is a hydrogen atom, or an acetyl, methoxymethyl, 1-ethoxyethyl, tert-butyldimethylsilyl or tert-butyldiphenylsilyl group are most preferable.

90     The compounds of this invention can roughly be grouped into the following three depending on the type of the substituent.

Group 1: a compound of formula (I) wherein X and Z together form  $=NO-$  and Y is a hydrogen atom, i.e., a compound of formula (IA)

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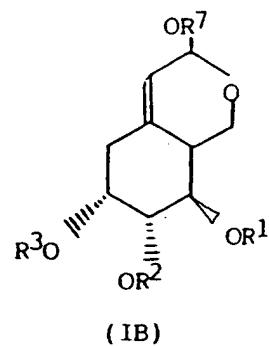


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110     Group 2: a compound of formula (I) wherein X and Z together form  $=CHCH(OR^7)O-$  or  $=CHCO_2-$  and Y is a hydrogen atom, i.e., a compound of formula (IB) or (IC)

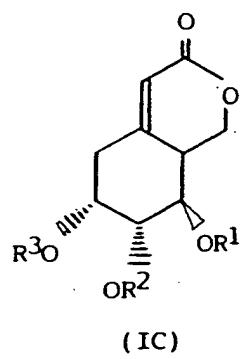
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10

or



(IC)

15 Group 3: a compound of formula (I) wherein X is an oxygen atom,  $=\text{CHCH}_2\text{OR}^4$ ,  $=\text{CHCHO}$ , or  $=\text{CHCO}_2\text{R}^5$ , Y is a hydrogen atom and Z is  $-\text{OR}^6$ , or Y and Z together form a single bond, i.e., a compound of formula (ID) or (IE)

In the following reaction scheme A, the compound of formula (I-1) belongs to group 1, the compounds of formulas (I-6) and (I-7) to group 2, and the compounds of formulas (I-2), (I-3), (I-4), (I-5), (I-8), (I-9) and (I-10) to group 3 respectively.

20 The cyclohexanetriol derivatives of this invention can be produced by an industrially easy reaction according to the following reaction scheme A using an inexpensive mannitol as a starting material.

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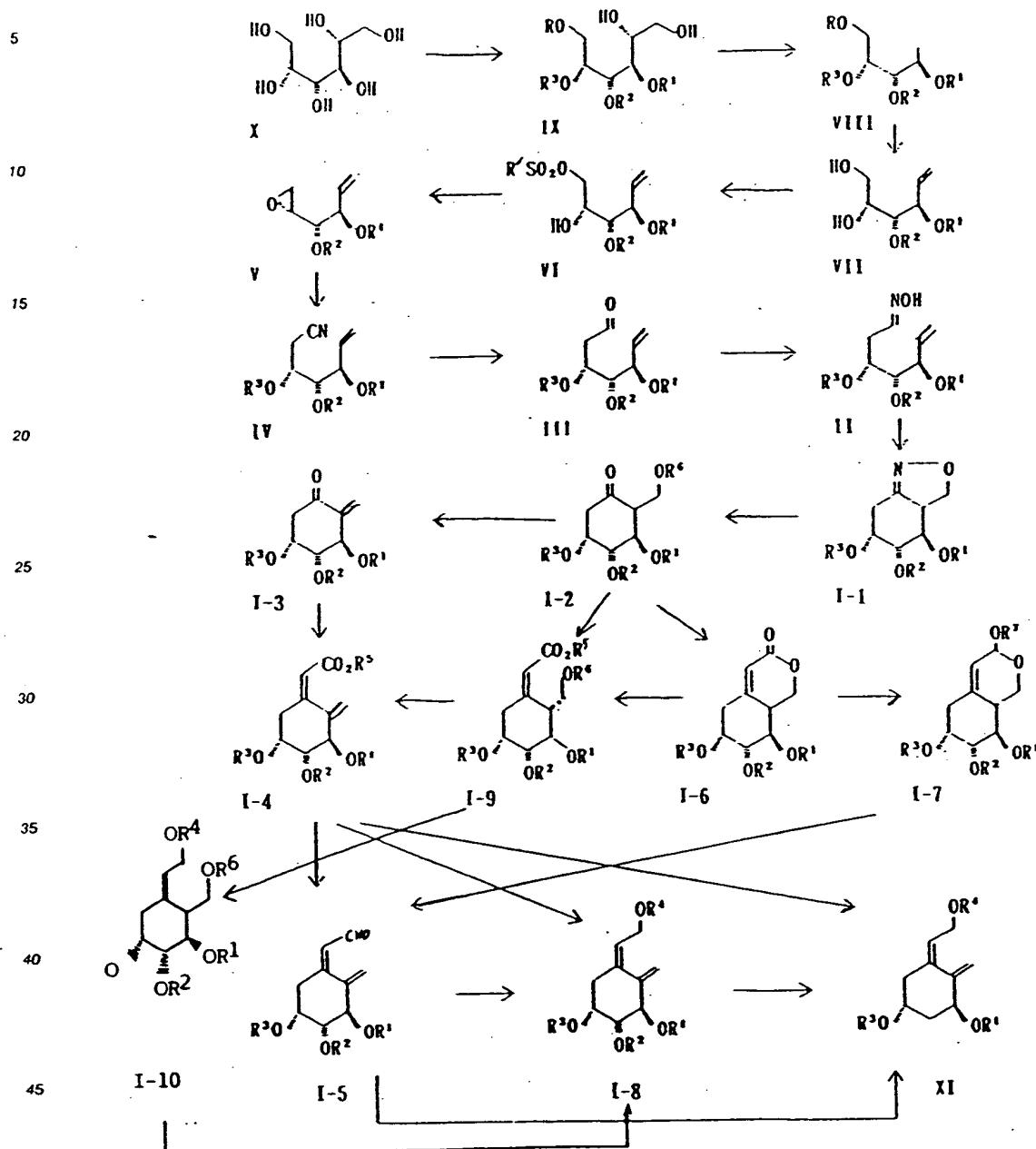
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Reaction scheme A

50 wherein

 $R^1, R^2, R^3, R^4, R^5, R^6$ , and  $R^7$  are as defined above, $R$  denotes a protecting group of a hydroxyl group, and $R'$  denotes an alkyl group (e.g., a methyl, ethyl or octyl group) or a substituted or unsubstituted aryl group (e.g., a phenyl, p-tolyl, p-chlorophenyl or naphthyl group).

55 The reactions in the respective steps of the above reaction scheme A will be described in more detail below.

A diol (IX) with protected hydroxyl groups in the 3-, 4-, 5- and 6-positions is formed from mannitol (X) in a usual manner. Then, said diol (IX) and 1 to 20 mols, per mol of the diol, of dimethylformamide

dimethylacetal, methyl orthoformate or ethyl orthoformate are heated at a temperature ranging from room temperature to about 200 °C in the presence or absence of an acid catalyst to obtain a cyclic orthoester. To this is added, as required, 1 to 10 mols of acid anhydride such as acetic anhydride, propionic anhydride or trifluoroacetic anhydride at temperatures ranging from at room temperature to about 200 °C. There is obtained a 5-hexene-1,2,3,4-tetraol derivative (VIII) with the hydroxyl groups protected.

The 5-hexene-1,2,3,4-tetraol derivative (VIII) with the hydroxyl groups protected is deprotected in a usual manner to obtain a 5-hexene-1,2,3,4-tetraol derivative (VII) with the 3- and 4-positions protected.

The 5-hexene-1,2,3,4-tetraol derivative (VII) with the 3- and 4-positions protected is converted into a 2,3,4-trihydroxy-5-hexen-1-yl monosulfonate derivative (VI) with the 3- and 4-positions protected by the reaction with 1 to 5 mols of a sulfonating agent such as p-toluenesulfonyl chloride or methanesulfonyl chloride at temperatures ranging from about -30 °C to about 80 °C in the presence of a base such as pyridine or triethylamine and in the presence or absence of an inert solvent.

The monosulfonate (VI) is converted into an epoxide in a usual manner. For example, said monotosylate is dissolved in an inert solvent such as methanol, ethanol or tetrahydrofuran, and the solution is reacted with a base such as sodium carbonate, potassium carbonate, sodium hydroxide or sodium hydride. There can result a 1,2-epoxy-5-hexene-3,4-diol derivative (V) with the 3- and 4-positions protected. Moreover, the 1,2-epoxy-5-hexene-3,4-diol derivative (V) can also be afforded by a known process using D-digitoxose or tartaric acid as a starting material [See, e.g., U. Kämpfner et al., Liebig's Ann. Chem., 1986, 1600-1609].

The epoxide (V) is converted into nitrile in a usual manner. For example, the epoxide is dissolved in an inert solvent such as methanol, ethanol, tetrahydrofuran or dimethylformamide, and the solution is reacted with a cyanating agent such as potassium cyanide, sodium cyanide or magnesium cyanide. If required, protection and deprotection of the hydroxyl groups are conducted. There can result 3,4,5-trihydroxy-6-heptenitrile or the substance with the hydroxyl groups protected (IV).

The obtained nitrile (IV) is, after protecting the hydroxyl groups if required, reduced with diisopropyl aluminum hydride or diisobutyl aluminum hydride in a usual manner to obtain 3,4,5-trihydroxy-6-heptenal or the substance with the hydroxyl groups protected (III).

The aldehyde (III) is reacted with hydroxylamine in a usual manner to obtain an oxime (II).

The thus obtained 3,4,5-trihydroxy-6-heptenal oxime (II) with the hydroxyl groups protected is dissolved in an inert solvent such as methylene chloride, chloroform, dichloroethane, toluene or dioxane, and the solution is reacted with 1 to 20 mols, per mol of said oxime, of an oxidizing agent such as a sodium hypochlorite aqueous solution or tert-butyl hypochlorite in the presence or absence of a catalyst such as triethylamine or pyridine at temperatures ranging from about -20 °C to about 30 °C. There can result a cyclohexanetriol derivative (I-1) wherein the obtained nitrile oxide causes 1,3-dipole cycloaddition.

The cyclohexanetriol derivative (I-1) is subjected to hydrogenolysis in an inert solvent such as methanol, ethanol or tetrahydrofuran or its mixture with water with a hydrogenation catalyst such as Raney nickel, palladium-carbon or platinum oxide in a hydrogen atmosphere and if required, in the presence of an acid such as boric acid or acetic acid, and is subjected to protection of the hydroxyl groups, if required. There can be obtained a cyclohexanetriol derivative (I-2).

The cyclohexanetriol derivative (I-2) can be converted into a cyclohexanetriol derivative (I-3) by dehydration in a usual manner.

Into the cyclohexanetriol derivative (I-3) is introduced an alkoxy carbonylmethylene group in a usual manner, e.g., by a Wittig-Horner reaction, and the geometry of the double bond is isomerized from trans to cis by a photosensitization reaction. There can be obtained a cyclohexanetriol derivative (I-4).

The ester portion of the cyclohexanetriol derivative (I-4) is reduced with diisobutyl aluminum hydride in a usual manner. There can be obtained a cyclohexanetriol derivative (I-5).

Moreover, the cyclohexanetriol derivative (I-4) or the cyclohexanetriol derivative (I-5) is reduced with diisobutyl aluminum hydride, lithium aluminum hydride, bismethoxyethoxyaluminum hydride, sodium borohydride, lithium borohydride or lithium triisobutyl aluminum hydride, and the hydroxyl groups are protected if required. There can result a cyclohexanetriol derivative (I-8).

Meanwhile, the hydroxyl group in the side chain of the cyclohexanetriol derivative (I-2) is esterified with phosphinoacetic acid using dicyclohexylcarbodiimide as a condensation agent, followed by an intramolecular Wittig-Horner reaction. There can be obtained a cyclohexanetriol derivative (I-6).

The ester portion of the cyclohexanetriol derivative (I-6) is reduced with diisobutyl aluminum hydride in a usual manner, and if required, acetalized with a lower alcohol. There can be obtained a cyclohexanetriol derivative (I-7).

The cyclohexanetriol (I-7) can be converted into cyclohexanetriol (I-5) by dehydration in a solvent mixture of a water-soluble solvent such as tetrahydrofuran, dioxane, methanol or ethanol and water in the presence of p-toluenesulfonic acid, sulfuric acid or hydrochloric acid.

Further, the cyclohexanetriol derivative (I-6) is reacted in a lower alcohol with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, barium hydroxide, sodium methoxide or sodium ethoxide, and if required, esterification and protection and deprotection of the hydroxyl groups are carried out. There can result a cyclohexanetriol derivative (I-9).

5 The cyclohexanetriol derivative (I-9) is dehydrated in a usual manner. There can result a cyclohexanetriol derivative (I-4). The dehydration can be conducted by a general method via sulfonation and halogenation; it can preferably be performed by a method via an organoselenium compound [see "Tetrahedron Letters", vol. 31, pp. 1577-1580 (1990)].

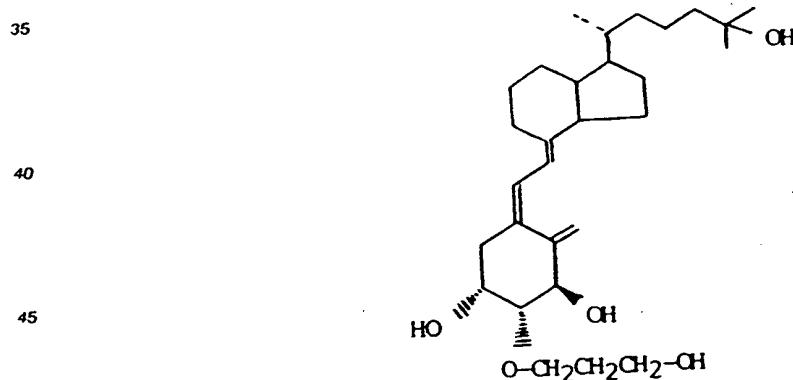
10 The cyclohexanetriol derivative (I-9) can also be afforded by reacting the cyclohexanetriol derivative (I-2) with silyl acetate and subjecting the reaction mixture to a Peterson reaction.

15 The ester portion of the cyclohexanetriol derivative (I-9) is reduced with a metal hydride such as lithium aluminum hydride or diisobutyl aluminum hydride in a usual manner and if required, the hydroxyl groups in the substance are protected. There can be obtained a cyclohexanetriol derivative (I-10).

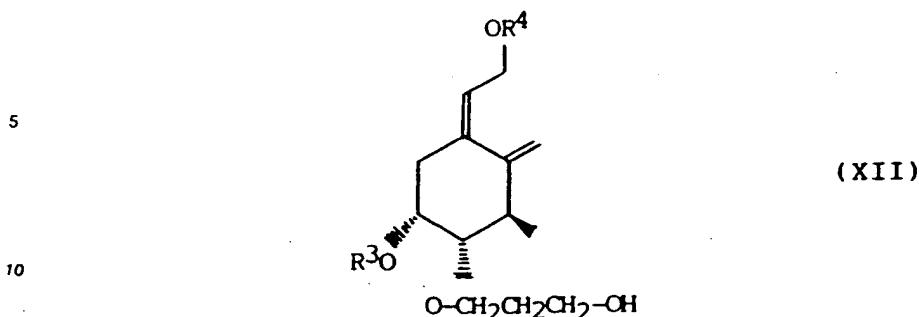
20 Isolation of the thus obtained cyclohexanetriol derivative (I) [the compounds of formula (I-1) to (I-10) in the reaction scheme A] from the reaction mixture and its purification are carried out in a manner ordinarily used in an organic reaction. For example, the reaction mixture is poured into ice water, extracted with an organic solvent such as diethyl ether, washed in sequence with dilute hydrochloric acid, a sodium hydrogen carbonate aqueous solution and a sodium chloride aqueous solution in this sequence, dried and concentrated to obtain a crude product. The crude product is purified by recrystallization and/or by chromatography as required. There can result a cyclohexanetriol derivative (I).

25 The thus obtained cyclohexanetriol derivative (I-8) can be converted into a cyclohexanediol derivative (XI) by sulfonylating the hydroxyl group in the 2-position thereof with methanesulfonyl chloride, p-toluenesulfonyl chloride or benzenesulfonyl chloride in the presence of triethylamine or pyridine, and then reducing the substance with lithium aluminum hydride or lithium triethylborohydride. The cyclohexanediol derivative (XI) is a known one as an A-ring synthon for producing a  $1\alpha$ -hydroxyvitamin D compound. It can be converted into the aforesaid various  $1\alpha$ -hydroxyvitamin D derivatives having pharmaceutical activity by a method known per se [see, e.g., E. G. Baggio et al., J. Am. Chem. Soc., 104, 2945-2948 (1982)].

30 Besides, since the cyclohexanetriol derivatives of this invention have the hydroxyl groups in not only the 1- and 3-positions but also the 2-position, they can advantageously be utilized as A-ring synthons for producing  $1\alpha$ -hydroxyvitamin D derivatives having the substituent in the 2-position upon making use of the hydroxyl group in the 2-position. For example,  $2\beta$ -hydroxypropoxy- $1\alpha$ ,  $25$ -dihydroxyvitamin  $D_3$  represented by the formula,



55 which is expected to be put to practical use as an osteoporosis treating agent having high blood durability as stated above, can be produced by introducing a 3-hydroxypropyl group into the hydroxyl group in the 2-position of the cyclohexanetriol derivative (I-8) of this invention to form a compound represented by formula (XII).



and then combining the compound with a CD ring synthon of 1 $\alpha$ -hydroxyvitamin D<sub>3</sub> in a manner known per  
15 se [see, e.g., E. G. Baggioini et al., J. Am. Chem. Soc., 104, 2945-2948 (1982)].

The following Referential Examples and Examples illustrate this invention more specifically. However,  
this invention is not limited thereto at all.

20 REFERENTIAL EXAMPLE 1

20 [Synthesis of 1,2:3,4-bis(dimethylmethylenedioxy)-5-hexene]

Two-hundred milliliters of N,N-dimethylformamide dimethylacetal were added to 128.5 g of 3,4:5,6-O-diisopropylidene-D-mannitol, and the mixture was heated at 100°C to remove methanol that formed.  
25 Heating continued at 100°C for 1 hour. After it was confirmed by thin layer chromatography that the starting material had almost disappeared, heating was conducted at 170°C, and excess N,N-dimethylformamide dimethylacetal was distilled off over about 1 hour. After the distillate disappeared, 100 ml of acetic anhydride was added gradually at 150°C to evaporate the distillate with the distillation temperature of about 90°C. The obtained reaction mixture was cooled to room temperature, and diethyl ether was added. The 30 organic layer was washed with a sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to provide 60.7 g of 1,2:3,4-bis(dimethylmethylenedioxy)-5-hexene having the following properties (yield 54%).

35 NMR spectrum (90MHz, CCl<sub>4</sub>)  $\delta$ : 5.90(ddd, 1H, J = 5.7, 10.2, 17.2Hz), 5.13-5.52(m, 2H), 4.37(ddt, 1H, J = 0.9, 5.7, 7.6 Hz), 3.8-4.2(m, 3H), 3.70(dd, 1H, J = 6.6, 7.6 Hz), 1.41(s, 9H), 1.34(s, 3H)

IR spectrum (neat, cm<sup>-1</sup>):

2984, 2932, 2880, 1455, 1378, 1250, 1214, 1154, 1120, 1065, 993, 924, 846, 512

Optical rotation:

40  $[\alpha]_D = 4.18^\circ$  (c = 2.00, CHCl<sub>3</sub>)

REFERENTIAL EXAMPLE 2

[Synthesis of 3,4-(dimethylmethylenedioxy)-5-hexene-1,2-diol]

45 Three-hundred milliliters of glacial acetic acid and 60 ml of water were added to 36.8 g of 1,2:3,4-bis(dimethylmethylenedioxy)-5-hexene obtained in Referential Example 1, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was then gradually added to 500 ml of a 50% sodium hydroxide aqueous solution filled with ice. Crystals of sodium acetate formed were filtered and washed with 50 methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to afford 13.5 g of 3,4-(dimethylmethylenedioxy)-5-hexene-1,2-diol having the following properties (yield 44%).

NMR spectrum (90MHz, CCl<sub>4</sub>)  $\delta$ :

5.93(ddd, 1H, J = 5.9, 9.1, 15.3Hz), 5.17-5.52(m, 2H), 4.42(dd, 1H, J = 5.9, 6.4Hz), 3.5-3.9(m, 4H), 3.0-3.4-55 (brs, 2H), 1.42(s, 6H)

IR spectrum (neat, cm<sup>-1</sup>):

3414, 2984, 2930, 2878, 1727, 1645, 1455, 1428, 1407, 1371, 1250, 1214, 1168, 1120, 1055, 925, 874, 812, 779, 734, 664, 621, 511

Optical rotation  
 $[\alpha]_D = +4.66^\circ$  (c = 1.07,  $\text{CHCl}_3$ )

## REFERENTIAL EXAMPLE 3

5 [Synthesis of 3,4-(dimethylmethylenedioxy)-2-hydroxy-5-hexen-1-yl p-toluenesulfonate]

3,4-(Dimethylmethylenedioxy)-5-hexene-1,2-diol (9.77 g) was mixed with 155 ml of pyridine and 52 ml of chloroform, and 11.39 g of p-toluenesulfonyl chloride was added gradually in four portions at 0°C. The 10 mixture was stirred at 0°C for 6 hours, poured into 6N hydrochloric acid with ice and extracted with diethyl ether. The extract was washed with a saturated sodium hydrogen carbonate aqueous solution and a saturated sodium chloride aqueous solution in sequence, dried with anhydrous ride aqueous solution in sequence, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to afford 17.88 g of 3,4-(dimethylmethylenedioxy)-2-hydroxy-5-hexen-1-yl p-toluenesulfonate having the following 15 properties.

NMR spectrum (90MHz,  $\text{CCl}_4$ )  $\delta$ :  
 7.80(d, 2H,  $J = 8.2\text{Hz}$ ), 7.35(d, 2H,  $J = 8.2\text{Hz}$ ), 5.87(ddd, 1H,  $J = 6.4, 8.9, 17.3\text{Hz}$ ), 5.15-5.49(m, 2H), 3.58-4.50(m, 5H), 2.45(s, 3H), 1.37(s, 6H)  
 IR spectrum (neat,  $\text{cm}^{-1}$ ):  
 20 3508, 3084, 3064, 2984, 2932, 2882, 1647, 1597, 1494, 1453, 1369, 1308, 1291, 1213, 1174, 1118, 1096, 1063, 980, 930, 896, 873, 834, 814, 691, 664, 552, 514

## REFERENTIAL EXAMPLE 4

25 [Synthesis of 1,2-epoxy-3,4-(dimethylmethylenedioxy)-5-hexene]

3,4-(Dimethylmethylenedioxy)-2-hydroxy-5-hexen-1-yl p-toluenesulfonate (17.88 g) was dissolved in 80 ml of methanol, and 17.11 g of anhydrous sodium carbonate was added at room temperature, followed by stirring the mixture for 15 minutes. The reaction mixture was filtered through Celite, and crystals were 30 washed with diethyl ether. After the filtrate was concentrated, the solid was filtered through a silica gel column. The filtrate was concentrated under reduced pressure to obtain 7.87 g of 1,2-epoxy-3,4-(dimethylmethylenedioxy)-5-hexene having the following properties.

NMR spectrum (90MHz,  $\text{CCl}_4$ )  $\delta$ :  
 5.90(ddd, 1H,  $J = 6.7, 9.8, 17.2\text{Hz}$ ), 5.2-5.52(m, 2H), 4.36(dd, 1H,  $J = 5.4, 6.7\text{Hz}$ ), 3.61(dd, 1H,  $J = 5.1, 5.4\text{Hz}$ ), 35 3.09(ddd, 1H,  $J = 2.6, 4.1, 4.9\text{Hz}$ ), 2.83(dd, 1H,  $J = 4.1, 4.9\text{Hz}$ ), 2.70(dd, 1H,  $J = 2.6, 4.9\text{Hz}$ ), 1.44(s, 6Hz)  
 IR spectrum (neat,  $\text{cm}^{-1}$ )  
 3520, 2984, 2928, 1725, 1659, 1597, 1494, 1454, 1358, 1306, 1290, 1250, 1212, 1188, 1176, 1120, 1095, 1071, 1003, 919, 876, 836, 816, 778, 713, 690, 663, 571, 554

## 40 REFERENTIAL EXAMPLE 5

[Synthesis of 4,5-(dimethylmethylenedioxy)-3-hydroxy-6-heptenenitrile]

45 Fifty milliliters of a saturated magnesium sulfate aqueous solution were cooled to 10°C, and 10.23 g of sodium cyanide was gradually added not to proceed over 10°C. After stirring at 10°C for 45 minutes, a solution of 7.61 g of 1,2-epoxy-3,4-(dimethylmethylenedioxy)-5-hexene in 30 ml of methanol was gradually added to the above mixture not to proceed over 10°C. After stirring at room temperature for 2 hours, the reaction mixture was extracted with ethyl acetate. The extract was washed with a sodium chloride aqueous solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained 50 residue was purified by silica gel column chromatography to afford 2.11 g of 4,5-(dimethylmethylenedioxy)-3-hydroxy-6-heptenenitrile having the following properties.

NMR spectrum (90MHz,  $\text{CCl}_4$ )  $\delta$ :  
 5.94(ddd, 1H,  $J = 7.6, 10.7, 18.3\text{Hz}$ ), 5.25-5.55(m, 2H), 4.40(dd, 1H,  $J = 7.6, 8.0\text{Hz}$ ), 4.08(m, 1H), 3.76(dd, 1H,  $J = 5.8, 7.7\text{Hz}$ ), 2.64(d, 1H,  $J = 5.9\text{Hz}$ ), 2.63(d, 1H, 6.4Hz), 2.46(brs, 1H), 1.42(s, 6H)  
 55 IR spectrum (neat,  $\text{cm}^{-1}$ ):  
 3446, 3086, 2986, 2934, 2982, 2250, 1645, 1456, 1411, 1372, 1215, 1168, 1121, 1068, 991, 933, 873, 810, 511

## REFERENTIAL EXAMPLE 6

[Synthesis of 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenenitrile]

5 Nine milliliters of diisopropylethylamine were added to 2.11 g of 4,5-(dimethylmethylenedioxy)-3-hydroxy-6-heptenenitrile, and 2 ml of methoxymethyl chloride was then added to the mixture gradually at 0°C. After stirring at 0°C for 16 hours, the reaction mixture was diluted with 300 ml of diethyl ether, and washed with 1N hydrochloric acid, a saturated sodium hydrogen carbonate aqueous solution and a sodium chloride aqueous solution in sequence. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was filtered by a silica gel column to afford 2.28 g of 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenenitrile having the following properties (yield 88%).

10 NMR spectrum (90MHz,  $\text{CCl}_4$ )  $\delta$ :  
 5.93(dd, 1H,  $J = 6.3, 10.2, 17.3\text{Hz}$ ), 5.16-5.52(m, 2H), 4.74(5, 2H), 4.35(dd, 1H,  $J = 6.6, 7.3\text{Hz}$ ), 3.78-4.00(m, 2H), 3.45(5, 3H), 2.60-2.80(m, 2H), 1.42(s, 6H)

15 IR spectrum (neat,  $\text{cm}^{-1}$ ):  
 2986, 2934, 2896, 2826, 2248, 1644, 1455, 1414, 1380, 1372, 1245, 1216, 1154, 1106, 1062, 1039, 992, 920, 875, 809, 512

## 20 REFERENTIAL EXAMPLE 7

[Synthesis of 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenal oxime]

4,5-(Dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenenitrile (159.8 mg) was dissolved in dry toluene, and 1.6 ml of 0.5N diisopropyl aluminum hydride was added at -78°C. The reaction mixture was stirred at -78°C for 2 hours and at -40°C for 30 minutes, and 5 % dilute sulfuric acid was gradually added at 0°C. The reaction mixture was diluted with diethyl ether, and the organic layer was washed with a sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, concentrated under reduced pressure to afford 91.1 mg of 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenal.

30 The above 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenal (91.9 mg) was dissolved in 1 ml of pyridine, and 45 mg of hydroxylamine hydrochloride was added at room temperature, and stirring was conducted at room temperature for 8 hours. The reaction mixture was diluted with diethyl ether. The diluted reaction mixture was washed with a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to afford 89.5 mg of 4,5-(dimethylmethylenedioxy)-3-methoxymethoxy-6-heptenal oxime having the following properties (yield 52%).

35 NMR spectrum (90MHz,  $\text{CCl}_4$ )  $\delta$ :  
 8.02(brs, 1H), 7.62(bs, 1H), 7.49(t, 1H,  $J = 6.4\text{Hz}$ ), 6.93(t, 1H,  $J = 5.4\text{Hz}$ ), 5.64-6.10(m, 2H), 5.16-5.00(m, 4H), 4.56-4.90(m, 4H), 4.24-4.48(m, 2H), 3.72-4.10(m, 4H), 3.39(5, 6H), 2.67(t, 2H,  $J = 5.7\text{Hz}$ ), 2.50(t, 2H,  $J = 5.9\text{Hz}$ ), 1.42(s, 12Hz)

40 IR spectrum (neat,  $\text{cm}^{-1}$ ):  
 3379, 3088, 2984, 2892, 2826, 1727, 1647, 1453, 1427, 1380, 1371, 1244, 1214, 1152, 1100, 1032, 991, 920, 876, 813, 705, 665, 512, 453

## 45 REFERENTIAL EXAMPLE 8

[Synthesis of 4,5-(dimethylmethylenedioxy)-3-(tert-butyldimethylsilyloxy)-6-heptenenitrile]

Two grams of tert-butyldimethylsilyl chloride were gradually added at 0°C to a solution comprising 2.11 g of 4,5-(dimethylmethylenedioxy)-3-hydroxy-6-heptenenitrile, 2.0 g of imidazole and 50 ml of methylene chloride. After stirring was conducted at room temperature for 16 hours, the reaction mixture was diluted with 300 ml of diethyl ether, and washed with 1N hydrochloric acid, a saturated sodium hydrogen carbonate aqueous solution and a sodium chloride aqueous solution in sequence. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to afford 2.63 g of 4,5-(dimethylmethylenedioxy)-3-(tert-butyldimethylsilyloxy)-6-heptenenitrile having the following properties (yield 79%).

FD mass spectrum:  $[\text{M}]^{+}$  311

